STEREOSELECTIVE CONTINUOUS-FLOW ALKYLATION OF ALDEHYDES IN ORGANOCATALYTIC PACKED-BED REACTORS

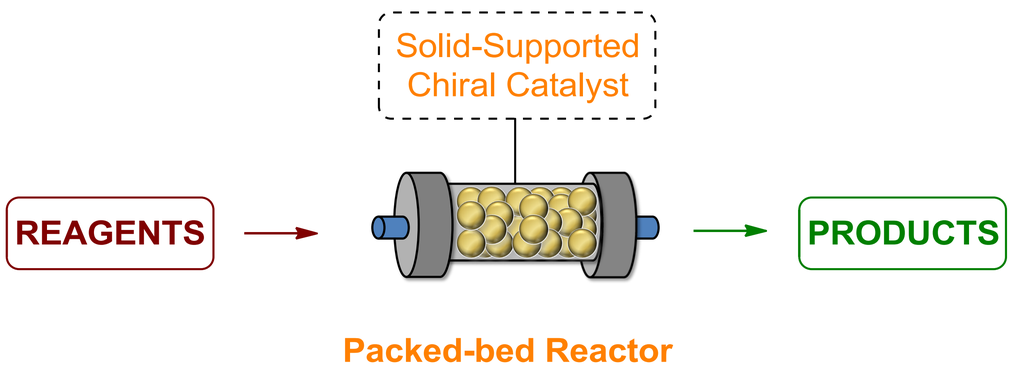
Riccardo Porta,[a] Maurizio Benaglia,[a] Alessandra Puglisi,[a] Pier Giorgio Cozzi[b]

[a]*Dipartimento di Chimica, Università degli Studi di Milano, via Golgi 19, 20133 Milano (Italy)*
[b]*Dipartimento di Chimica "G. Ciamician", Università di Bologna, via Selmi 2, 40126 Bologna (Italy)*

e-mail: riccardo.porta@unimi.it

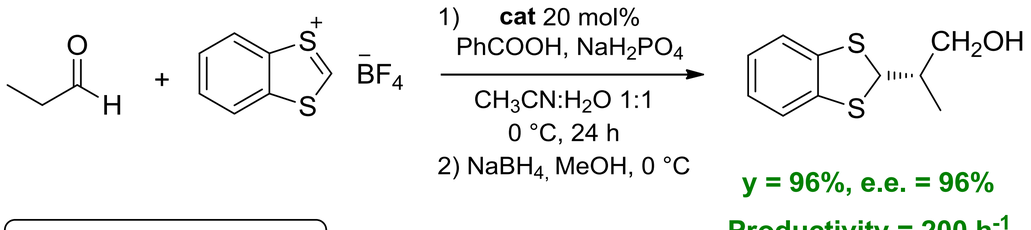
Flow Chemistry

The practice of performing chemical reactions under flow conditions has risen significantly in recent years, allowing the development of sustainable, safe and efficient processes, as well as an easier scale-up and a more accurate control of reaction conditions with respect to batch procedures. Additionally, the combination with solid-supported catalysts allows the reuse of the catalytic species avoiding the recovery and recycle step.[1]



Enantioselective Aldehydes α-Alkylation

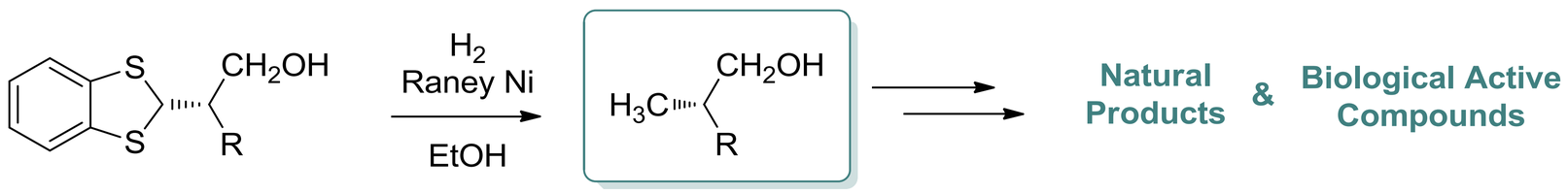
The development of an efficient catalytic enantioselective α-alkylation of carbonyl compounds has been a challenging task for a long time. Among the strategies to perform this reaction, the novel synthetic methodology employing stable carbenium ions, promoted by MacMillan imidazolidinone chiral organocatalyst, proved to be a reliable reaction to obtain α-alkylated products in high yields and great enantiomeric excesses.[3]



$$\text{Productivity} = \frac{mmol\ product \times 1000}{mmol\ catalyst \times time}$$

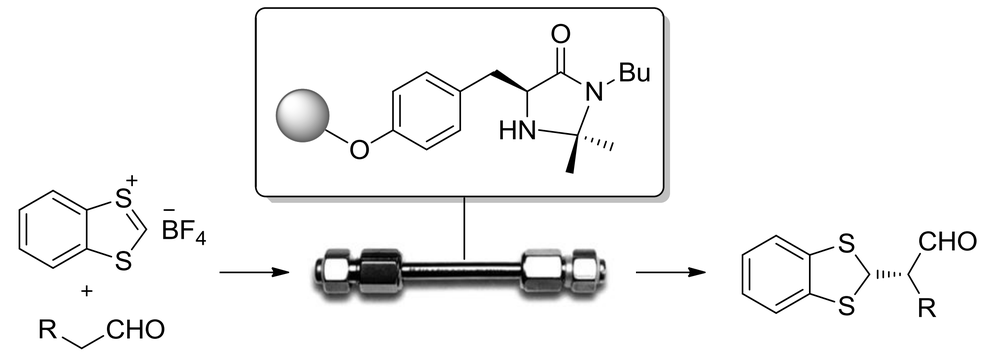
Synthetic Applications

Alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate offers the possibility to perform a reductive removal of benzodithiolyl moiety thus affording enantioenriched α-methyl derivatives, key intermediates for the synthesis of natural products and biological active compounds.[4]



Organocatalytic Packed-bed Reactors

The enantioselective α-alkylation of aldehydes with benzodithiolylium tetrafluoroborate promoted by chiral imidazolidinones was studied. Reagents were fed continuously through a Syringe Pump to two packed-bed reactors (**R1** and **R2**) filled with polystyrene-supported and silica-supported MacMillan catalysts.[2]
Stainless steel HPLC columns (length = 6 cm, V_i = 0,75 cm^3) were used as "homemade" continuous-flow reactors.

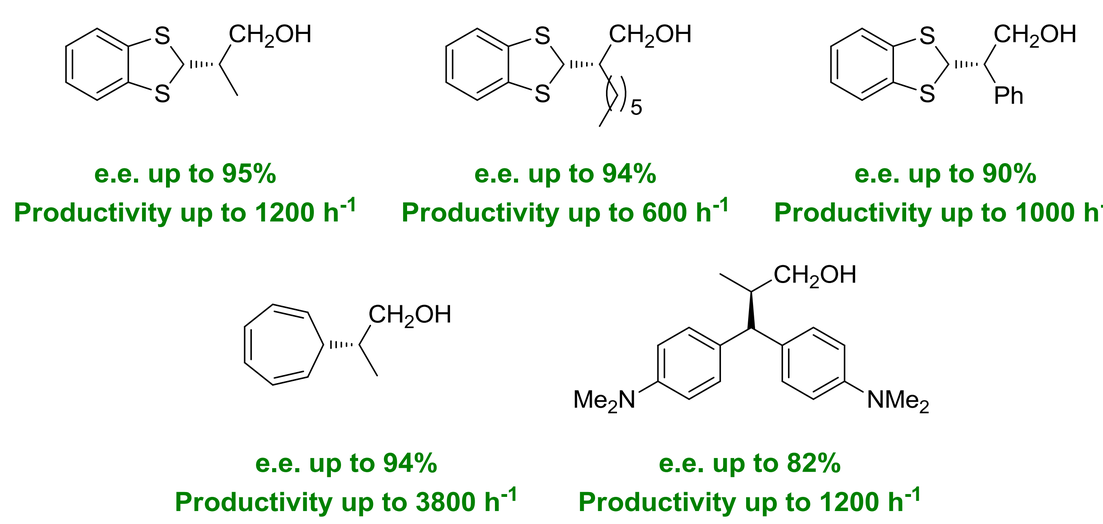


R1: Polystyrene (prepared by polymerization of imidazolidinone monomer, divinylbenzene, AIBN, toluene and dodecanol)

R2: Silica (prepared by grafting of imidazolidinone monomer onto commercial silica)

Continuous-Flow Alkylations

The first example of stereoselective alkylation of aldehydes *in continuo* was developed. Excellent enantiomeric excesses and remarkable productivity were achieved at room temperature, showing the great applicability of the continuous-flow system. Best results were obtained with polystyrene packed-bed reactor **R1**.



Flow-rates ranging from 0,1 to 10 mL/h were employed; residence times of 4 minutes only were reached thus leading to high productivity without affecting the stereoselectivity.

References:

[1] (a) Puglisi, A.; Benaglia, M.; Chiroli, V. *Green Chem.* **2013**, *15*, 1790; (b) Tsubogo, T.; Ishiwata, T.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 6590; (c) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38; (d) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun*. **2011**, 4583; (e) *Microreactors in Organic Synthesis and Catalysis*, Wirth, T.; Ed. Wiley-VCH: Weinheim, **2008**.

[2] (a) Chiroli, V.; Benaglia, M.; Puglisi, A.; Porta, R.; Jumde, R. P.; Mandoli, A. *Green Chem*. **2014**, *16*, 2798; (b) Porta, R.; Benaglia, M.; Chiroli, V.; Coccia, F.; Puglisi, A. *Isr. J. Chem* **2014**, *54*, 381; (c) Puglisi, A.; Benaglia, M.; Annunziata, R.; Chiroli, V.; Porta, R.; Gervasini, A. *J. Org. Chem.* **2013**, *78*, 11326.

[3] Gualandi, A.; Emer, E.; Capdevila, M. G.; Cozzi, P. G. *Angew. Chem. Int. Ed.* **2011**, *50*, 7842.

[4] Gualandi, A.; Canestrari, P.; Emer, E.; Cozzi, P. G. *Adv. Synth. Catal.* **2014**, *356*, 528 and references cited therein.